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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/777,920	02/07/2001	Jacques Dumas	BAYER 15 P3	6183

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EXAMINER	
DESAI, RITA J	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/777,920	DUMAS ET AL.	
	Examiner	Art Unit	
	Rita J. Desai	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5,9,10,12,14-18,25,27,29,30,34-37,39,40,42 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5, 9, 10, 12, 14-18, 25, 27, 29, 30, 34-37, 39, 40, 42, 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims pending 2-5, 9,10, 12, 14-18,25, 27, 29, 30,34-37, 39, 40, 42, 45-49.

The rejection of the claims 2-5, 9, 10, 12, 14-18, 25, 27, 29, 30, 34-37, 39, 40, 42, 45-49 under 35 USC 112 first para still stands.

The breadth of the claim as written is very large.

The generic language of the substituents does not clearly define the scope of the claims.

There is no test data given to indicate that these compounds do inhibit RAF kinase.

The only compounds made which are in the elected group are the ones given in table 7.

These compounds have Ra and Rb to be H or alkyl.

Applicants definition is very generic. Such as

a)
independently hydrogen; ~~or ~ olected Irom the group consletmg o~~~-tSt0 alKyl, CI-CI0 alkoxy, Cs-lo cycloalkyl, C2.10 alkenyl, C~-10 alkenoyl, C6-t2 aryl, Cs-12 hetaryl which is a 5-12 carbon atom aromatic ring system of 1-3 rings, at least one of which is aromatic, in which 1-3 carbon atoms are replaced by having 1 3 heteroatoms selected from O, N and S, 5-6 membered Cs-12 eycloalkyl having 0-3 heteroatoms selected from N, S and O, ~~€~~a4aralkyl, ~~C~~C~~atkary~~substituted C1-10 alkyl, substituted CH0 alkoxy, substituted 5-6 membered Cs-10 eycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted Ct-lz aryl, substituted C3-12 hetaryl which is a 5-12 carbon atom aromatic ring system of 1-3 rings, at least one of which is aromatic, in which 1-3 carbon atoms are replaced by having 1 3 heteroatoms selected from N, S and O, ~~~ub~tituted~~C;~a4 ~~aralkyl, ~ub~tituted~~C~24 ~~alkaryl,~~where Ra and Rb are a substituted group, they are substituted by halogen up to per halo, hydroxy, CH0 alkyl, 5-6 membered Cs-12 cycloalkyl having 0-3 heteroatoms selected from O, S and N, C3-~2 hetaryl which is a 5-12 carbon atom aromatic ring system of 1-3 rings, at least one

cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C3-CI~_ hetaryl which is a 5-12 carbon atom aromatic ring system of 1-3 rings, at least one of which is aromatic, in which 1-3 carbon atoms are heteroatoms selected from N S and O, up to per halo hetaryl,

Also the claims "substituted" does not even clearly say what it is substituted with.

In re Cavillito and Grey, 134 USPQ 370. Lower aliphatic was held unacceptable in Cavallito due to the need to provide adequate representative exemplification in the specification for all manner and degree of unsaturation and cyclization to provide a basis of support in the specification for "aliphatic" and unknown substitution.

It is unclear from the claims what is encompassed.

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)
It was shown in evidence and by way of admissions elicited by the defendants from the plaintiff before trial that one skilled in the art of organic chemistry may start in the group of the acetic acid radical and the radicals of homologues of acetic acid to which the patent relates, for instance, with the simple hydrocarbon called methane and theoretically progress along the series in the general group called alkanes from one substance to another by increasing the size of the molecules in steps of one carbon atom and two hydrogen atoms. At least formulas for such substances, as well as for others, can be written in an indefinite chain. Also it was shown that for the hydrogen atoms of the alkane molecules the atoms of what are called halogens may be substituted and so may the atoms of other groups including the residue of the hydrocarbon benzene. The latter is represented in chemical formulas by a hexagon which is called the benzene ring and, as changes in the atomic structure of the molecule occur, the ones introduced take varying positions within the ring which positions determine the nature of the compound.
Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected.

Ex parte DIAMOND, 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

Scope of claims should not be unduly extensive in chemical fields where applicability is highly speculative or not explored; subject matter which relies upon prediction for its support is unpatentable.
Specification contains 23 specific examples, but they are to preparation of relatively simple compounds; this is relatively meager and non representative disclosure to support claims embracing millions of compounds.

Applicant may not preempt unduly large field by expedient of making broad prophetic statements in specification and claims unless accuracy of such statements is sufficiently supported by well established chemical principles or by sufficient number of examples.
"The term 'substituted' without modification or restriction includes all compounds wherein one or more of the atoms or radicals of the original compound have been replaced by one or more other atoms or radicals. Without any limitation on the character or number of substituents it becomes apparent that the quoted term may be considered inclusive of almost any possible substance and the claims under consideration are either of unlimited or indeterminate scope. We are of the opinion that the reasoning of the courts in Schering Corp. v. Gilbert, 68 USPQ 84, and Hercules Powder Co. v. Rohm & Haas, 70 USPQ 297, is controlling."
embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637.
In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court held that "An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class."

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In addition *In re Fouche* 169 USPQ 429 dealt with a similar issue with respect to how to use

requirement of 112 1st paragraph,

"Inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention; nevertheless, applicant must use some technique of providing teaching of how to use which is commensurate with breadth of protection sought by claim, unless such knowledge is already available to persons skilled in the art; thus, where applicant undertakes to define invention by recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of group.
Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic

invention. Nevertheless, an applicant must use *some* technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art.
It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group. The examiner and the board did not believe that appellant had done so as to the heterocyclic members of the group. While they noted the absence of examples using heterocyclic moieties, we do not find that they viewed examples as mandatory. The issue before us is whether appellant has provided *any* teaching of how to use compounds containing the heterocyclic members of the Markush group. The only reference to heterocyclic radicals in the specification is the statement that "the invention provides" compounds of the structure shown in claim 1, wherein Z may be, among other possibilities,
a mononuclear, nitrogen-containing heterocycle connected to the chain A by the nitrogen atom, and optionally containing an oxygen, sulphur, or second nitrogen atom in the ring and optionally substituted by one of more alkyl radicals containing 1 to 5 carbon atoms each, such as 1-pyrrolidyl, piperidino, morpholino, 1-piperazinyl, or 4-alkyl-1-piperazinyl. "

Claims employing generic language at the point of novelty, such as applicants', neither provide those elements required to practice the inventions, nor "inform the public" during the life of the patent of the limits of the monopoly asserted. The expression could encompass myriad of compounds and applicants claimed expression represents only an

invitation to experiment regarding possible compounds.

In re Kirk, 153 USPQ 48. If you the "public" find that it works, I claim it, is not a proper basis of patentability.

Applicants should, in return for a 20 year monopoly be disclosing to the public that which can be actually demonstrated fact.

Further, applicants claims are drawn to a biological activity in a host. That of inhibiting Raf kinase.

State of the art is such that even a small change changes the activity considerably.

In Aza-Stilbenes … by McDonald et al 2006, see page 5380.

> Structure–activity relationships generated via the initial screening set suggested di-substitution ortho to the stilbene was important for enzyme activity. Maintaining a hydrogen in the 4-position of the pendant phenyl ring and the *N*-methyl amide on the pyridyl ring, Table 2, we synthesized a set of stilbenes to probe the SAR in this region. The diethyl substitution **16** was 100-fold less active than the parent, indicating a size restriction. Replacement of the methyl groups by chlorines, **17**, resulted in a compound that was equipotent with **13** in the enzyme assay. Removal of one of the methyl or chloro groups, **18** and **19**, proved to be 10-fold less active than the parent **13**. Interestingly, when only one of methyl groups was replaced with chlorine, as in **20**, the activity was increased by about 3-fold.

It clearly shows that even when a substituent such a Cl and methyl change positions or are absent the activity changes considerabley.

Applicants claims have a generic group (by the way which may be further substituted and it is not clear with what) , so the structure is not clearly defined and the state of the activity is very unpredictable.

Also applicants have not provided any data. There is no IC50 value even in assays.

The in vivo assay description in the specifications is drawn to treating tumors. There is no daa given and tumor treatment (cancer) is very hard to predict .

In vivo – cancer

Those of skill in the art recognize that in-vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlation s are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assays does not permit a single extrapolation of in vitro assays to human diagonistic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known that in the art that cultured cells over a period of time , lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further , although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that , "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 yrs. Clearly it is well known in the art that cells i culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host –tumor and cell-cell interactions.

CORRELATION: IN VITRO /IN VIVO

The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must

weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Thus in view of the limited guidance provided and the state and unpredictability in the chemical art it cannot be seen how applicants claims are enabled.

The rejection is being repeated here.

The rejection of the claims 2-5,9,10, 12, 14-18,25, 27, 29, 30,34, 37, 39, 40, 42, 45-49 under 35 USC 112 first paragraph scope of enablement still stands.

Even though applicants have deleted the Rx , Ry and Rz the Rx is still NRaRb which includes

R_c is R_a or NR_aR_b where R_a and R_b are,

a) independently hydrogen, or selected from the group consisting of C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from O, N and S, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_7-C_{24} alkaryl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C_{6-12} aryl, substituted C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} aralkyl, substituted C_{7-24} alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl[[,]] or halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, ~~or $-C(O)R_a$~~;

W is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_3-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, C_6-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C_1-C_{10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_2-C_{10} alkenyl, substituted C_3-C_{10} alkenoyl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C_6-C_{12} aryl, substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected

from O, N and S, substituted C_7-C_{24} aralkyl, substituted C_7-C_{24} alkaryl, and substituted C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S;

each R^7 is independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_2-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected form O, N and S, up to per-halosubstituted C_6-C_{14} aryl, up to per-halosubstituted C_7-C_{24} aralkyl, up to per-halosubstituted C_7-C_{24} alkaryl, and up to per-halosubstituted C_4-C_{23} alkheteroaryl; and

each Z is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$ $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C_1-C_{10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkenoyl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C_6-C_{12} aryl, substituted C_7-C_{24} alkaryl, substituted C_7-C_{24} aralkyl and substituted C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S; wherein if Z is a substituted group, the one or more substituents are selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$.

As it can be seen from the above the terms have a very generic description with C7-C24 aralkyl, C4-C23- alkylheteroaryl, C3-C13 heteroaryl being some of them. The generic definition having 1-3 heteroatoms selected from N, O or S is also indefinite because with all the permutations and combinations it is not clear what the meets and bounds of the claims are.

Applicants argue that the Side Reactions is a general statement and hasnothing to do with their compounds, this is incorrect. The Preface in the Side Reactions is the state of the Art indicating how difficult it is to synthesize compounds.

Also Pages 8 and 9 of the same book indicates how similar starting materials under same conditions give different products. This is the state of the art. Making compounds with different substitutents is not simply putting everything together and expect that it would form similar compounds.

Examples of closely related starting materials which upon treatment with the same reagents yield completely different products are sketched in Scheme 1.6. The additional methyl group present in the second starting material skews addition to the carbonyl group of the radical formed by ring scission of the cyclobutane ring, and thus prevents ring expansion to the cyclohexanone. Removal of the methoxycarbonyl group leads to cleavage of a different bond of the cyclobutane ring and thereby again to a different type of product [12].

When the state of the art is so unpredictable , applicants need to provide much more guidance than just say that these generic substitutent are within the scope of their compounds.

Only compound 104 and compounds in table 7 have been made on page 103.

In all the compounds Ra Rb are either a H or an alkyl.

None of the species made have any group other that that.

So with the amount of unpredictability in the art and limited amount of disclosure, it would certainly require and undue amount of burden to make and use these compounds.

Even though the Rx is drawn to one substituent NRaRb the definition of Ra and Rb is so vague with generic terms that it is impossible to decipher the full scope let alone make and use them.

With limited guidance of Ra and Rb being a H or an alkyl it would be burdensome and more than routine experimentation for one of skill in the art to make and use these compounds.

Applicants argue that

"The specification here provides both general and specific guidance for synthesizing the ureas claimed with over one hundred syntheses described on pages 56-80 and over 35 pages of specific synthesis steps that can be used to prepare the claimed compounds (pages **17-56),** some with complex ring structures. There is no evidence this disclosure is lacking in any way. "

This is incorrect. Only one example C5 on page 56 which would fall within the elected group.

And in this compound , Ra and Rb are H and a methyl.

This one example does not commensurate with the scope of the claims.

Thus the rejection still stands.

Applicants claims 27, 29 , 30, 35, 47, 48 are drawn to a method f of treating that too a solid tumors /cancers. No data has been provided. An experiment according to Monica et al is stated on page 106, however no data has been provided.

The state of the art is that one drug cannot treat all the various cancers.

Yet without showing any data and any guidance applicants claim treating all tumors and cancers.

This is an undue amount of burden as it is not known that a drug can treat all cancers.

Conclusion

Claims 2-5, 9, 10, 12, 14-18, 25, 27, 29, 30, 34-37, 39, 40, 42, 45-49 stand rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rita J. Desai
Primary Examiner
Art Unit 1625

R.D.
June 25, 2008

/Rita J. Desai/
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